DOI:
10.1016/j.jval.2019.08.001

Document Version
Peer reviewed version

Citation for published version (APA):
Hazra, N. C., Rudisill, C., Jackson, S. H., & Gulliford, M. C. (2019). Cost-Effectiveness of Antihypertensive Therapy in Patients Older Than 80 Years: Cohort Study and Markov Model. *Value in Health*, *22*(12), 1362-1369. https://doi.org/10.1016/j.jval.2019.08.001

Cost-effectiveness of anti-hypertensive therapy over the age of 80 years: Cohort study and Markov model

Journal:	*Value in Health*
Manuscript ID	VIH-2018-1015.R1
Article Type:	Economic Evaluation
Health Areas List:	Aging < Health Areas, Antihypertensive < Health Areas, Cardiovascular Disease < Health Areas, Geriatrics / Aging < Health Areas, Hypertension < Health Areas
Methods of Interest List:	Economic: Markov model < Methods of Interest, Economic: Observational data < Methods of Interest, Health Policy: modeling study < Methods of Interest, Health Policy: database study < Methods of Interest
Keywords Enter Your Own:	

Cost-effectiveness of anti-hypertensive therapy over the age of 80 years: Cohort study and Markov model

Running title: Population-Based Cohort Study and Markov Model

Precis (25 word summary): Anti-hypertensive treatment in over-80s is estimated to be highly cost-effective, even if the health benefits are lesser or side effects costlier than the base case.

Financial Disclosure: None reported.

Word Count: 3860

Number of Pages: 24

Number of Figures: 3

Number of Tables: 2

ABSTRACT

Background: Blood pressure and anti-hypertensive treatment generally increase with age but there is uncertainty concerning the value of treatment at very advanced ages.

Objectives: To estimate cost-effectiveness of anti-hypertensive treatment (AHT) in people aged 80 years and over.

Methods: A Markov model compared AHT with no blood pressure treatment for prevention of cardiovascular disease. Outcomes were new stroke, coronary heart disease and diabetes, with falls included as a potential complication of AHT. Costs were evaluated from a health system perspective. Incidence, mortality and costs of health care utilisation were estimated from linked primary and secondary care electronic health records for 98,220 individuals aged 80 and older. Clinical effectiveness estimates were from the Hypertension in the Very Elderly Trial (HYVET). Deterministic and probabilistic sensitivity analyses were conducted.

Results: In the base case, AHT was associated with an additional 725 quality adjusted life years (QALYs) and £4.3 million per 1000, with an incremental cost-effectiveness ratio (ICER) of £5977 per QALY. The ICER was most sensitive to the cost of falls and relative risk reduction in stroke incidence. Probabilistic sensitivity analysis gave 95% uncertainty intervals: £5057 to £8398 per QALY in men and £4955 to £8218 per QALY in women. AHT for secondary prevention in participants with CHD gave an ICER of £9903 per QALY.

Conclusions: AHT is estimated to be cost-effective in individuals aged 80 years and over, even if health benefits are smaller or side effects costlier than in the base case. Benefits and harms for vulnerable sub-groups require further evaluation.

Highlights

What is already known about the topic?

- Blood pressure levels and treatment with anti-hypertensive therapy (AHT) increase with age but there is uncertainty concerning the value of treatment at very advanced ages beyond 80 years.

What does the paper add to existing knowledge?

- AHT in over-80s was associated with 725 incremental quality adjusted life years (QALYs) and incremental health care costs of £4.3 million per 1000, resulting in an incremental cost-effectiveness ratio (ICER) of £5977 per QALY. The ICER estimate was sensitive to the costs of treatment-associated falls but AHT was considered cost-effective in over-80s even if side effects are more costly than in the base case.

What insights does the paper provide for informing health care-related decision making?

- Treatment for hypertension over the age of 80 years is cost-effective after accounting for falls, with a high probability of health benefit at acceptable cost even under less favourable assumptions. These findings may contribute new information to inform guidelines for treating hypertension in over-80s.

INTRODUCTION

High blood pressure (BP), or clinical hypertension, is the most important risk factor for cardiovascular diseases (CVDs) including stroke, heart failure and myocardial infarction [1 2]. Blood pressure levels generally increase with age [3 4] and the prevalence of hypertension and treatment with antihypertensive therapy (AHT) is very high in older adults, despite uncertainties concerning the risks and benefits of treatment at advanced ages.[5 6] The occurrence of CVD has also shifted to older ages. CVDs now represent one of the most costly disease categories, with direct costs of $555 billion in the United States (US) in 2016 and £19 billion annually in the United Kingdom (UK).[7 8]

While many studies have provided evidence of the effectiveness of AHT for cardiovascular prevention in middle-aged adults, the evidence at older ages is less clear. Several studies have reported benefits of AHT in people over 60 years, particularly for prevention of stroke, [9-12] but potential benefits in people aged over 80 years are less well-established. The HYpertension in the Very Elderly Trial (HYVET) [13] is the only placebo-controlled trial to evaluate the effectiveness of AHT in participants aged 80 years or older. The HYVET trial provided evidence of reduction in stroke incidence and mortality, as well as lower all-cause mortality, with AHT. [13] Eligible participants in HYVET may have had less comorbidity than in a general population sample of older adults but the HYVET investigators found no evidence that the intervention effect depended on frailty level. [14] In the Systolic Blood Pressure Intervention Trial (SPRINT), which employed a treat-to-target BP strategy in participants aged 75 and over, AHT was associated with lower rates of CVD events and lower all-cause mortality, but intervention was associated with slightly higher rates of kidney injury and syncope.[15] Non-randomised epidemiological studies report that comorbidity and frailty are frequent in this age-group, consequently adverse effects including orthostatic hypotension and falls assume greater importance at older ages.[5 16] Many authors emphasize the importance of considering adverse events, cautioning against aggressive BP-lowering in the very elderly.[17 18]

Guidelines for treating hypertension in older people are inconsistent. The American Heart Association (AHA) and American College of Cardiology (ACC) recently recommended that the threshold systolic blood pressure (SBP) level for initiating treatment in over-65s should be reduced from 140 mm Hg to 130 mm Hg. [19 20] In contrast, the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) recommend the SBP threshold of 150 mm Hg in over-60s [21], consistent with the National Institute for Care Excellence (NICE) recommendations in the UK for over-80s.[22] In the absence of sufficient evidence, it is uncertain which individuals should be classified as hypertensive and treated with AHT. Improved evidence on the cost-effectiveness of AHT in over-80s may help to inform this debate.

One previous health economic evaluation [23] was conducted in the age-group over 80 years, evaluating cost-effectiveness of AHT from a Swiss health care perspective. This Swiss study used life-years as its main health outcome and concluded that treatment was cost-effective. However, the data available for analysis suffered from several limitations. The study did not estimate quality adjusted life years as a preferred outcome; costs were extrapolated from studies in younger age-groups; and adverse events were not accounted for. The present study aimed to add to this limited evidence base, by estimating the cost-effectiveness of AHT in individuals aged 80 years and older. The study draws on empirical data from the UK through epidemiological analysis of electronic health records. These analyses provided population-based estimates for the probability of transitioning between each of the model's health states.

Analyses also provided empirical estimates for health care resource use. Potential adverse events from treatment were accounted for in the model through the inclusion of falls.

METHODS

Intervention comparators

Cost-effectiveness of universal AHT, using a diuretic and an ACE-inhibitor if needed, was evaluated in comparison with no AHT. A population-wide strategy in which all individuals over 80 years are treated is justified by clinical guidelines, which generally recommend that treatment for hypertension should be based on individuals' overall 10-year CVD risk.[19 22 24-26] Increasing age is the strongest predictor of risk, with all individuals aged 80 years and older generally being classified at high-risk; though not all existing risk scores are designed to be applicable at advanced ages.[27]

Model structure

A Markov model was designed including five health states: 'At risk', 'Coronary Heart Disease' (CHD), 'Stroke' (STR), 'Type 2 Diabetes Mellitus' (DM) and 'Dead'. Each state was further subdivided by single year of age and gender (Figure 1). Falls associated with AHT were accounted for in each cycle of the model as a potential adverse event in very elderly populations.

Patient population and subgroup analyses

The base-case modelled population was gender stratified (35% males and 65% females) according to the composition of the over-80 CPRD population and the United Nations World Population Ageing estimates.[28] Subgroup analyses were conducted by varying the starting age and gender distribution in the model. The cost-effectiveness of AHT for secondary prevention was evaluated in a start population with CHD.

Data sources

Data used to populate the model were derived from epidemiological analysis of primary care electronic health records data from a cohort of participants registered with the UK's Clinical Practice Research Datalink (CPRD). The CPRD is a nationally representative sample of approximately 680 primary care practices across the UK. Health care utilisation and costs, including prescriptions, were estimated for each health state from CPRD electronic health records, with linked secondary care Hospital Episode Statistics (HES) data. [29 30] A systematic review was conducted to obtain data for treatment effectiveness in the model.

Epidemiological and costing analyses

Age-specific estimates of incidence, mortality and costs for each health state were estimated from a cohort of 98,220 participants aged 80 years and older drawn from analysis of electronic health records with linked hospital episodes data. [30 31] These analyses provided empirical estimates to underpin the model that are broadly representative of the UK's over-80 population, including representation of frail and multi-morbid individuals. The study cohort provided 200,719 person-years for epidemiological and costing analysis at 80-89 years, 95,431 person-years at 90-99 years, and 4,544 person-years at 100 years and older. Rates of incidence and mortality were estimated in a time-to-event framework using a Weibull survival model, providing transition probabilities for movement between health states in the Markov model (Supplementary Table 1). Variance estimates from the Weibull model were also be incorporated into a probabilistic sensitivity analysis (PSA) to assess uncertainty in the model. Survival analyses were completed using CPRD data from 2001-14.

Costs were estimated based on utilisation of primary care services in CPRD (general practice consultations, telephone consultations, home visits, emergency and out-of-hours consultations) and secondary care services in hospital episodes statistics (inpatient hospital admissions, outpatient visits, day case visits and emergency admissions), including prescriptions (Supplementary Table 2). Unit costs were derived from the NHS reference costs and the Personal Social Services Research Unit (PSSRU). A two-part regression model was employed, as reported previously [30], to determine mean annual costs for each health state, stratified by age. Falls costs were estimated similarly through epidemiological analysis of falls incidence and costs of falls in CPRD and HES, including all costs associated with a fall in a given year. This includes health care costs associated with any potential fractures following a fall.

Intervention effects and unit costs

Clinical effectiveness measures for over-80s were drawn from the HYVET trial (Supplementary Table 3). Treatment was associated with a 30% relative risk (RR) reduction in the rate of stroke (RR = 0.70, 95% CI: 0.49 to 1.01), a 39% reduction in the rate of stroke mortality (RR = 0.61, 95% CI: 0.38 to 0.99), a 34% reduction in CHD (RR = 0.66, 95% CI: 0.53 to 0.82), and a 21% reduction (RR = 0.79, 95% CI: 0.65 to 0.95) in all-cause mortality.[32 33] It was assumed that any improvement in diabetes mortality was equivalent to the improvement in all-cause mortality, as these data for over-80s were not available. Based on systematic review evidence, we assumed no effect of AHT on diabetes incidence in the base-case analysis, but a 19% reduction (RR=0.81, 95% CI 0.62 to 1.06) in diabetes incidence [34] was employed in a sensitivity analysis from a sample aged greater than 65 years, in the absence of any data for over-80s.

The relative incidence of experiencing a fall, between treated and not treated individuals, was applied to the model based on a non-randomised epidemiological study by Tinetti et al.[16] in the absence of trial data. Based on Tinetti et al., AHT was associated with a 40% relative increase in falls (RR = 1.40, 95% CI: 1.03 to 1.90) among a nationally representative sample of adults aged 70 years and older in the US, providing a conservative estimate for the model.

Intervention costs of treatment with AHT were estimated at £51.87 per year using the British National Formulary and the CPRD drug dictionary, based on the drugs used in HYVET. Unit costs of primary care consultations were: GP consultation, £45; telephone consultation, £27; home consultation, £88.92; out-of-hours consultation, £45 [35]. Secondary care consultations included: day case, £721; inpatient, £2729.64; outpatient, £275; accident & emergency, £132.[36]

Time horizon and discounting

All outcomes were modelled using a lifetime horizon with a one-year cycle length. Both costs and health outcomes were discounted at an annual rate of 3.5% [37].

Model outcomes

Health outcomes were valued using quality-adjusted life-years (QALYs) and utility values used to calculate QALYs were drawn from data published in a compendium of EuroQol five-dimensional (EQ-5D) questionnaire utility values for the UK participants by health condition and age (Supplementary Table 4) [38]. Costs (£, GBP) are presented from a health system perspective, adopting any health care, medical care and drug costs borne by the UK National Health Service.

Sensitivity analysis

To characterise uncertainty, a univariate sensitivity analysis was conducted to assess the individual impact of changes in input parameters on the resulting ICER [39]. Values were varied primarily based on 95% confidence intervals for parameter estimates. An alternative cost for falls was employed using a previously published estimate of cost in the 12 months following a fall [40], assuming that most excess costs would occur in the year after a fall.

A probabilistic sensitivity analysis was also conducted by applying distributional assumptions to each parameter, representing statistical uncertainty across all model inputs simultaneously, and randomly selecting values across 10,000 simulations. Annual transition probabilities for the model were obtained by sampling from normal distributions using EHR-derived estimates as inputs. Beta distributions were employed for utility data and gamma distributions for cost data [41]. Relative risks were sampled using a lognormal distribution.

Model validation

Model validation comprised face validity (setting parameters to extreme values to assess predictable effects on outputs), internal validity (consistency of results across software platforms, Excel and R) and external validity (review by external experts). The base case model was built in both Excel and R, while the probabilistic sensitivity analyses was run in R for improved computational time.

Ethics

The use of fully anonymized CPRD data was approved by the Medicines and Healthcare products Regulatory Agency's Independent Scientific Advisory Committee (Protocol number 15_047).

RESULTS

In the base case, the model start population comprised 1,000 individuals aged 80 years without long-term conditions, including 650 women and 350 men. AHT was associated with an overall increase of 725 QALYs per 1000 individuals entering the model, compared to no treatment, with 7,025 lifetime QALYs per 1000 (4,731 for females, 2,294 for males) in the treatment group and 6,300 lifetime QALYs per 1000 (4,256 for females, 2,044 for males) in the control group (Table 1). AHT was associated with an increased cost of £4.3 million per 1000 individuals compared to no treatment, with costs equating to £32.4 million per 1000 in the treatment group (£21.2 million for females, £11.2 million for males) and £28.1 million in the control group (£18.4 million for females, £9.7 million for males). The cost of falls amounted to £1.1 million per 1000 in the treatment group and £684,542 per 1000 in the control group, indicating higher falls cost in those taking AHT compared to those not on AHT. AHT, in comparison with no treatment, was associated with a decrease in the number of life-years lived with CHD and stroke, but an increase in the number of years lived with diabetes resulting from longer duration survival with AHT. The additional lifetime health care costs per 1000 associated with an increase of 23.6 person years lived with diabetes were £125,482 (£750,522 in the treatment arm and £625,040 in the control arm).

For an 80-year old individual, the additional lifetime cost of anti-hypertensive treatment was £4,334 for an additional 0.725 QALYs gained. The estimated incremental cost-effectiveness ratio (ICER) (lifetime cost per QALY) for AHT in the base-case was £5,977 per QALY

(Table 1). Considering the UK's willingness-to-pay (WTP) threshold range of £20,000-30,000 per QALY, AHT can be considered cost-effective in over-80s even after accounting for the costs of adverse events through falls. While treatment appeared to be slightly less cost-effective for males than females, the ICERs for both were still well below the UK's threshold range (£5,910 per QALY in females; £6,105 per QALY in males). If the WTP threshold were £30,000 per QALY, the net monetary benefit (NMB) to the health service associated with AHT in over-80s is valued at approximately £17.4 million per 1000 individuals, or £10.2 million if each QALY gained is valued at £20,000 (Table 1).

Characterising uncertainty

In a one-way sensitivity analysis, cost-effectiveness was most sensitive to changes in the cost of falls (Figure 2). Despite varying this most influential parameter in the model, the ICER remained below the threshold range for cost-effectiveness. Increasing the annual falls cost from £1,300 in the base case to £6,696 in the deterministic sensitivity analysis resulted in an increased ICER of £8,364 per QALY. The relative risk reduction for stroke was also an influential model parameter. When varying this value to indicate a smaller difference in stroke rates between groups, the ICER increased to £7,058 per QALY, also remaining cost-effective. With a lower limit of 0.49, indicating a greater stroke reduction with treatment, the ICER decreased to £5,287 per QALY. Changes in the discount rate and utility values had minimal effect on cost-effectiveness, as the ICER remained between £5,887 and £6,111 per QALY with variations in these parameters. Sensitivity of the ICER to selected input parameters is summarised in Figure 2.

Probabilistic sensitivity and subgroup analysis

The base-case probabilistic model for over-80s yielded an ICER of £6,146 per QALY (95% uncertainty interval (UI) £5,291 to £7,446), and subgroup analysis indicated slightly greater cost-effectiveness in females (£6,074 per QALY, 95% UI £4,955 to £8,218) compared to males (£6,281 per QALY, 95% UI £5,057 to £8,398) (Table 2). Uncertainty intervals represent the 95% range for estimates from all simulations. Incremental differences in costs and QALYs between comparator groups for 10,000 simulations are presented in a cost-effectiveness plane (Figure 3, left panel). With all points falling below the £30,000 per QALY and £20,000 per QALY thresholds, treatment remained cost-effective after accounting for distributional uncertainty in all model parameters.

When evaluating older age sub-groups, the ICER remained below the threshold for cost-effectiveness, at £6,521 per QALY in over-90s and £5,759 per QALY in over-100s. Treatment was most cost-effective in centenarians overall (95% UI £5,025 to £7,071). AHT was more cost-effective for females over 80 and 90 years, but cost-effectiveness was greater for males over 100 years.

AHT for secondary prevention of CVDs was less cost-effective compared to primary prevention, with an ICER of £9,903 per QALY (95% UI £9,364 to £12,322) in over-80s and £11,102 per QALY in over-90s. While primary prevention with AHT was more cost-effective than treatment for secondary prevention, both can be considered cost-effective options based on the UK's threshold range. Age-specific cost-effectiveness acceptability curves summarise uncertainty in the estimates of cost-effectiveness by age (Figure 3, right panel). AHT proved to be cost-effective in all age-groups 100% of the time, with the probability of being cost-effective equal to 1.00 (over-80s and over-100s) or 0.999 (over-90s) at a WTP threshold of £30,000 per QALY.

DISCUSSION

This research drew on empirical electronic health records data to model the cost-effectiveness of AHT in individuals aged 80 years and older. The study incorporated several novel aspects. This is the first study in this age-group to incorporate quality of life by using QALYs as an outcome measure to evaluate cost-effectiveness of AHT. The only other existing economic evaluation of AHT in over-80s used life years as its main health outcome in a Swiss context.[23] Our model is also the first of its kind to account for falls as a potential adverse event in the evaluation of cost-effectiveness, a significant concern and cost driver in the very elderly. Increased QALYs associated with treatment resulted from lower incidence of CHD and stroke and reduced cardiovascular mortality. Higher costs in the treatment group arose primarily from increased longevity associated with AHT, but also from increased falls costs captured as an adverse consequence of treatment at advanced ages.

AHT was highly cost-effective in this older age-group aged 80 years and over, even after accounting for uncertainty in all model parameters. This conclusion should be cautiously limited to relatively fit over-80s, as our estimates for treatment effectiveness originate from HYVET participants with few comorbidities and low levels of frailty. Treatment was more cost-effective in centenarian men compared to women, likely because they incur less incremental cost increase from treatment as a result of being typically healthier with less chronic morbidity compared to female centenarians.[42-44]

Cost-effectiveness was most sensitive to the relative risk for stroke and all-cause mortality estimates, and the cost of falls. Falls costs are difficult to measure at a population level because falls have wide ranging spectrums of severity and subsequent treatment or follow-up after an event can vary greatly. This will depend on the nature and scale of the fall (e.g.

impact on hip, head, femur, wrist) and the health status of the older individual experiencing the fall such as whether they experience multi-morbidity or polypharmacy. Despite the importance of falls in older populations, the cost of falls has not previously been incorporated in economic models evaluating the cost-effectiveness of AHT in the elderly, potentially indicating the scarcity of available data for this parameter.

Strengths and limitations

While economic evaluations are a widely used method to make trade-offs between costs and outcomes more explicit, these studies are scarce in over-80s for all treatment areas as there are less representative epidemiological data to inform estimates specific to this age-group. Findings from this study hold the strengths of using population-based nationally representative epidemiological data from a severely understudied elderly age-group. This allowed for empirical estimates to underpin the model that are broadly representative of the UK's over-80 population, including partial representation of frail and multi-morbid individuals.

The study is limited mostly by a scarcity of effectiveness and utility data specific to the general population of individuals over 80. Only one placebo-controlled trial has been conducted in this age-group, and mean utilities were attained for younger ages with an age decrement applied to extrapolate age-specific utilities beyond 80 years of age. Using this decrement approach for utilities may represent a limitation, as later years of life may not always correspond to decreases in quality of life, as we reported previously.[31 44] This was however accounted for in sensitivity analyses where this age decrement was only applied up to 95 years, and did not have a large impact on the ICER. We did not assume a utility decrement associated with falls because of the high variability in falls outcomes. In addition, there was no available falls disutility in the literature based on a generic preference-based measure that would consider all possible clinical outcomes. This approach is consistent with a previous cost-effectiveness model of bariatric surgery, where the cost of complications but not disutility associated with the complications were included because of a lack of data.[45]

This model did not include comorbidity health states, but this will be partially accounted for in the underlying population-based estimates of the model where existing comorbidities will be equally impactful in both groups. While we included the impact of falls incidence, we did not model any possible impact on renal function. Blood pressure lowering may sometimes contribute to renal insufficiency but AHT is also expected to reduce age-related decline in renal function. As with most economic evaluations, our model represented a simplification of the clinical reality. There are benefits from opting for less complex health economic models, to minimise the inevitable uncertainty based on data inputs.

Given the estimates of treatment effect that underpin our model originate from HYVET, there are concerns regarding the generalisability of this evidence from a carefully selected group of older participants. Participants from HYVET were subject to several exclusions and are likely to be healthier than the general elderly hypertensive population. Hypertension treatment at the advanced age of 80 and older is often delivered in the context of frailty, multiple morbidity and polypharmacy and these vulnerable individuals are not fully represented in the trial data. Data from HYVET were used for all individuals in the model up to 100 years and over. We acknowledge that only 4.6% of HYVET patients were aged 90 years or over, but this trial currently provides the best available effectiveness data for modelling the cost-effectiveness of AHT; trial effectiveness data are not presently available for centenarians as a sub-group. All other estimates underpinning the model were obtained from a representative population-based sample of over-80s, offering age-specific values of incidence and mortality rates up to 100 years and over, as well as age-specific costs, potentially offsetting these generalisability concerns. Additional sensitivity analysis also allowed for a wide range of uncertainty estimates.

Conclusions and what this study adds

Despite the importance of potential harms from medicines in over-80s, previous economic evaluations on AHT in this age-group have not incorporated adverse events, likely due to scarcity of data. This model acknowledges the additional costs of potential side effects from AHT use in the elderly, which may often result in falls from syncope, orthostatic hypotension and dizziness.

Our model adds to the limited existing literature by, firstly, using population-based UK estimates, secondly, accounting for adverse events through falls and, thirdly, using quality of life data allowing for QALYs to be used as the main health outcome measure in the model. The use of QALYs in our model allows decision makers to compare our findings with results from other clinical areas to make health care coverage decisions across a range of clinical areas. This study also demonstrates the cost-effectiveness of taking a population-based approach to condition management with age being the first indicator of treatment followed by decision-making around frailty rather than a more elaborate risk assessment process.

Improved evidence concerning possible adverse outcomes of AHT in vulnerable older sub-groups is still needed. As frailty levels increase, there may be more adverse events, fewer life expectancy gains, and lower incremental costs of AHT. There remains a need to estimate effectiveness of AHT at different levels of frailty before determining cost-effectiveness in more vulnerable sub-groups of older people.

REFERENCES

1. Forouzanfar MH, Alexander L, Anderson HR, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386(10010):2287-323. doi: 10.1016/s0140-6736(15)00128-2 [published Online First: 2015/09/15]
2. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/s0140-6736(12)61689-4 [published Online First: 2012/12/19]
3. Pinto E. Blood pressure and ageing. *Postgrad Med J* 2007;83(976):109-14. doi: 10.1136/pgmj.2006.048371
4. Zhao Y, Yan H, Marshall RJ, et al. Trends in population blood pressure and prevalence, awareness, treatment, and control of hypertension among middle-aged and older adults in a rural area of Northwest China from 1982 to 2010. *PloS one* 2013;8(4):e61779. doi: 10.1371/journal.pone.0061779 [published Online First: 2013/04/25]
5. Benetos A, Rossignol P, Cherubini A, et al. Polypharmacy in the Aging Patient: Management of Hypertension in Octogenarians. *JAMA* 2015;314(2):170-80. doi: 10.1001/jama.2015.7517 [published Online First: 2015/07/15]
6. Stott DJ, Applegate WB. Perspectives on hypertension treatment in older persons. *Age Ageing* 2018:afy055. doi: 10.1093/ageing/afy055
7. American Heart Association. Cardiovascular disease: a costly burden for America - projections through 2035, 2017.
8. British Heart Foundation. Cardiovascular Disease Statistics: BHF UK Factsheet, 2018.
9. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991;265(24):3255-64. [published Online First: 1991/06/26]
10. Amery A, Brixko R, Clement D, et al. Efficacy of antihypertensive drug treatment according to age, sex, blood pressure, and previous cardiovascular disease in patients over the age of 60. *Lancet* 1986;328(8507):589-92. doi: https://doi.org/10.1016/S0140-6736(86)92424-4
11. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350(9080):757-64. doi: https://doi.org/10.1016/S0140-6736(97)05381-6
12. Musini VM, Tejani AM, Bassett K, et al. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev* 2009(4):CD000028. doi: 10.1002/14651858.CD000028.pub2 [published Online First: 2009/10/13]
13. Beckett NS, Peters R, Fletcher AE, et al. Treatment of Hypertension in Patients 80 Years of Age or Older. *N Engl J Med* 2008;358(18):1887-98. doi: 10.1056/NEJMoa0801369
14. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC medicine* 2015;13:78. doi: 10.1186/s12916-015-0328-1 [published Online First: 2015/04/17]

15. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. *Jama* 2016;315(24):2673-82. doi: 10.1001/jama.2016.7050 [published Online First: 2016/05/20]
16. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine* 2014;174(4):588-95. doi: 10.1001/jamainternmed.2013.14764
17. Conroy SP, Westendorp RGJ, Witham MD. Hypertension treatment for older people-navigating between Scylla and Charybdis. *Age Ageing* 2018 doi: 10.1093/ageing/afy053 [published Online First: 2018/05/23]
18. Wilt TJ, Kansagara D, Qaseem A. Hypertension Limbo: Balancing Benefits, Harms, and Patient Preferences Before We Lower the Bar on Blood Pressure. *Annals of internal medicine* 2018;168(5):369-70. doi: 10.7326/m17-3293 [published Online First: 2018/01/23]
19. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *J Am Coll Cardiol* 2018;71(19):e127.
20. Krumholz HM. Blood pressure guidelines as starting point in clinical decisions. *BMJ* 2018;360
21. Qaseem A, Wilt TJ, Rich R, et al. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: A clinical practice guideline from the american college of physicians and the american academy of family physicians. *Annals of internal medicine* 2017;166(6):430-37. doi: 10.7326/M16-1785
22. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management [CG127], 2016.
23. Szucs TD, Waeber B, Tomonaga Y. Cost-effectiveness of antihypertensive treatment in patients 80 years of age or older in Switzerland: an analysis of the HYVET study from a Swiss perspective. *J Hum Hypertens* 2010;24(2):117-23. doi: 10.1038/jhh.2009.47
24. British Hypertension Society. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;328(7445):926. doi: https://doi.org/10.1136/bmj.328.7445.926
25. Williams B, Poulter NR, Brown MJ, et al. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;328(7440):634-40.
26. Fuster V, Gambús F, Patriciello A, et al. The polypill approach – An innovative strategy to improve cardiovascular health in Europe. *BMC Pharmacol Toxicol* 2017;18:10. doi: 10.1186/s40360-016-0102-9
27. Carlson E, Kipps M, Thomson J. Influences on the food habits of some ethnic minorities in the United Kingdom. *HumNutrApplNutr* 1984;38(2):85-98.
28. United Nations. World Population Ageing 1950-2050: Population Division, DESA, United Nations, 2002.
29. Gulliford MC, Charlton J, Prevost T, et al. Costs and Outcomes of Increasing Access to Bariatric Surgery: Cohort Study and Cost-Effectiveness Analysis Using Electronic Health Records. *Value in Health* 2017 doi: 10.1016/j.jval.2016.08.734
30. Hazra NC, Rudisill C, Gulliford MC. Determinants of health care costs in the senior elderly: age, comorbidity, impairment, or proximity to death? *The European Journal of Health Economics* 2017 doi: 10.1007/s10198-017-0926-2

31. Hazra NC, Gulliford MC. Evolution of the "fourth stage" of epidemiologic transition in people aged 80 years and over: population-based cohort study using electronic health records. *Popul Health Metr* 2017;15(1):18. doi: 10.1186/s12963-017-0136-2
32. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *New Engl J Med* 2008;358(18):1887-98. doi: http://dx.doi.org/10.1056/NEJMoa0801369
33. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *J Hypertens* 2010;28(7):1366-72. doi: http://dx.doi.org/10.1097/HJH.0b013e328339f9c5
34. Padwal R, Mamdani M, Alter DA, et al. Antihypertensive Therapy and Incidence of Type 2 Diabetes in an Elderly Cohort. *Diabetes Care* 2004;27(10):2458-63.
35. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2015. Kent: The University of Kent, 2015.
36. Department of Health. National schedule of reference costs: the main schedule, 2014-15, 2015.
37. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013, 2013.
38. Sullivan PW, Slejko JF, Sculpher MJ, et al. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making* 2011;31(6):800-4. doi: 10.1177/0272989x11401031 [published Online First: 2011/03/23]
39. York Health Economics Consortium. Univariate/One Way Sensitivity Analysis York2016. [Available from: http://www.yhec.co.uk/glossary/univariateone-way-sensitivity-analysis/ accessed Oct 24 2017.]
40. The King's Fund. Exploring the system-wide costs of falls in older people in Torbay, 2013.
41. Gray A, Clarke PM, Wolstenholme JL, et al. Applied Methods of Cost-effectiveness Analysis in Healthcare. New York, NY: Oxford University Press 2010.
42. Evert J, Lawler E, Bogan H, et al. Morbidity Profiles of Centenarians: Survivors, Delayers, and Escapers. *J Gerontol A* 2003;58(3):M232-M37. doi: 10.1093/gerona/58.3.M232
43. Franceschi C, Motta L, Valensin S, et al. Do men and women follow different trajectories to reach extreme longevity? Italian Multicenter Study on Centenarians (IMUSCE). *Aging (Milan, Italy)* 2000;12(2):77-84. [published Online First: 2000/07/21]
44. Hazra NC, Dregan A, Jackson S, et al. Differences in Health at Age 100 According to Sex: Population-Based Cohort Study of Centenarians Using Electronic Health Records. *J Am Geriatr Soc* 2015;63(7):1331-37. doi: http://dx.doi.org/10.1111/jgs.13484
45. Gulliford MC, Charlton J, Prevost T, et al. Costs and Outcomes of Increasing Access to Bariatric Surgery: Cohort Study and Cost-Effectiveness Analysis Using Electronic Health Records. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2017;20(1):85-92. doi: 10.1016/j.jval.2016.08.734 [published Online First: 2017/02/19]

Table 1: Results from base-case deterministic model per thousand persons.

	Treatment	No Treatment	Incremental
Total discounted costs			
Overall	£32,447,727	£28,113,532	£4,334,196
Females	£21,224,916	£18,413,859	£2,811,057
Males	£11,222,812	£9,699,673	£1,523,139
Total discounted QALYs			
Overall	7,025	6,300	725
Females	4,731	4,256	476
Males	2,294	2,044	249
Incremental Cost-Effectiveness Ratio			
Overall		£5,977 per QALY	
Females		£5,910 per QALY	
Males		£6,105 per QALY	
WTP threshold	**Net Monetary Benefit (per 1,000 treated)**		**Net Health Benefit (per 1,000 treated)**
£30,000 per QALY	£17,415,804		580.5 QALYs
£20,000 per QALY	£10,165,804		508.3 QALYs

WTP = willingness to pay

Table 2: Incremental cost-effectiveness ratios (UK £ per QALY) and 95% uncertainty intervals from subgroup and probabilistic sensitivity analysis

	Incremental cost-effectiveness ratio (95% uncertainty interval, UK£ per QALY)		
	80 years and over	**90 years and over**	**100 years and over**
Base-case model			
Overall	6,146 (5,291 to 7,446)	6,521 (5,772 to 7,829)	5,759 (5,025 to 7,071)
Females only	6,074 (4,955 to 8,218)	6,410 (5,417 to 8,605)	5,880 (4,846 to 8,509)
Males only	6,281 (5,057 to 8,398)	6,736 (5,672 to 8,678)	5,557 (4,681 to 7,600)
Secondary prevention			
Overall	9,903 (9,364 to 12,322)	11,102 (10,503 to 13,421)	11,003 (10,396 to 13,167)
Females	9,727 (8,960 to 14,459)	10,846 (8,816 to 15,466)	10,876 (9,874 to 15,297)
Males	10,244 (9,599 to 14,130)	11,598 (9,492 to 15,171)	11,231 (10,316 to 14,506)

Legend for Figure 1: Schematic diagram of age-stratified Markov model. CHD, Coronary Heart Disease; STR, Stroke; DM, Diabetes Mellitus.

Legend for Figure 2: Tornado diagram of univariate sensitivity analysis. RR, relative risk; STR, stroke; CHD, coronary heart disease; DM, diabetes mellitus.

Legend for Figure 3: Cost-effectiveness plane and cost-effectiveness acceptability curve.

Supplementary Table 1: Survival models (incidence and mortality) for age- and gender-specific transition probabilities using CPRD data

Transition	Regression model[a]
Healthy to CHD	$y = -18.4 - 0.36x + 0.33z - 0.002z^2$
Healthy to STR	$y = -7.3 - 0.11x + 0.03z$
Healthy to DM	$y = -43.8 - 0.22x + 1.1z - 0.008z^2$
Healthy to Dead	$y = -11.3 - 0.28x + 0.10z$
CHD to Dead	$y = 1.61 - 0.29x - 0.16z + 0.001z^2$
STR to Dead	$y = -6.44 - 0.13x + 0.06z$
DM to Dead	$y = 23.75 - 0.29x - 0.73z + 0.005z^2$

[a] x = Gender (female = 2, male = 1); z = Age

Supplementary Table 2: Costs (UK £) of health care utilisation (including prescriptions) for Markov model from CPRD

	Females (mean)	Males (mean)
Healthy		
80-84	2815	3123
85-89	3502	3884
90-94	4051	4460
95-99	4488	4891
100+	3705	3754
Coronary Heart Disease		
80-84	4085	4635
85-89	5032	5702
90-94	5807	6509
95-99	6516	7254
100+	6179	6609
Stroke		
80-84	4433	5150
85-89	5419	6316
90-94	6222	7114
95-99	6940	7798
100+	6521	6993
Diabetes Mellitus		
80-84	3818	4487
85-89	4783	5567
90-94	5539	6427
95-99	6288	7071
100+	6898	5896
Falls		
All ages		1299.70

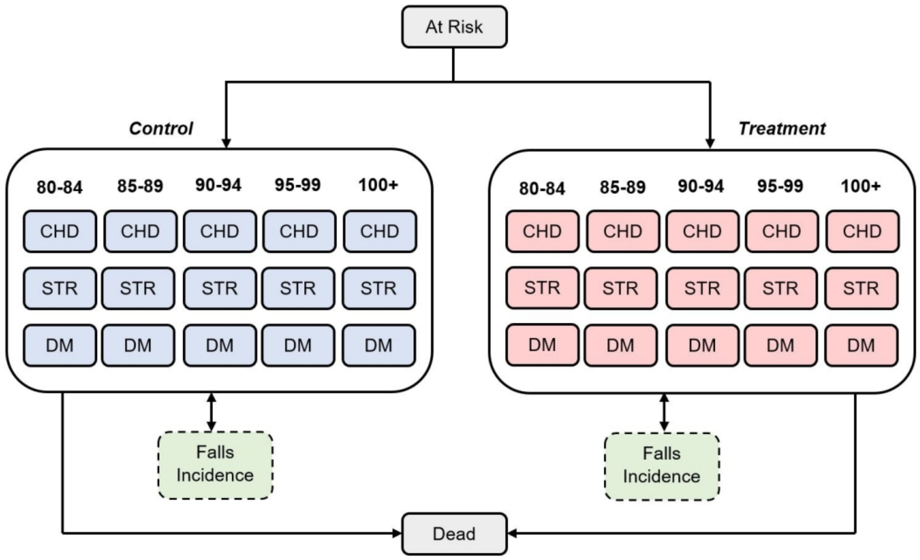
Supplementary Table 3: Intervention effects for Markov model

Condition	Mean Relative Risk (RR)	95% CI	Source
Incidence			
Coronary heart disease	0.66	0.53 to 0.82	*Beckett et al. 2008 (HYVET Main Trial)*
Stroke	0.70	0.49 to 1.01	*Beckett et al. 2008 (HYVET Main Trial)*
Diabetes mellitus	1.00	1.00 to 1.00	*N/A*
Falls	1.40	1.03 to 1.90	*Tinetti et al. 2014*
Mortality			
Coronary heart disease	0.77	0.60 to 1.01	
Stroke	0.61	0.38 to 0.99	*Beckett et al. 2008 (HYVET Main Trial)*
Diabetes mellitus	0.79	0.65 to 0.95	
All cause death	0.79	0.65 to 0.95	

Supplementary Table 4: Utility values for health states used in the model

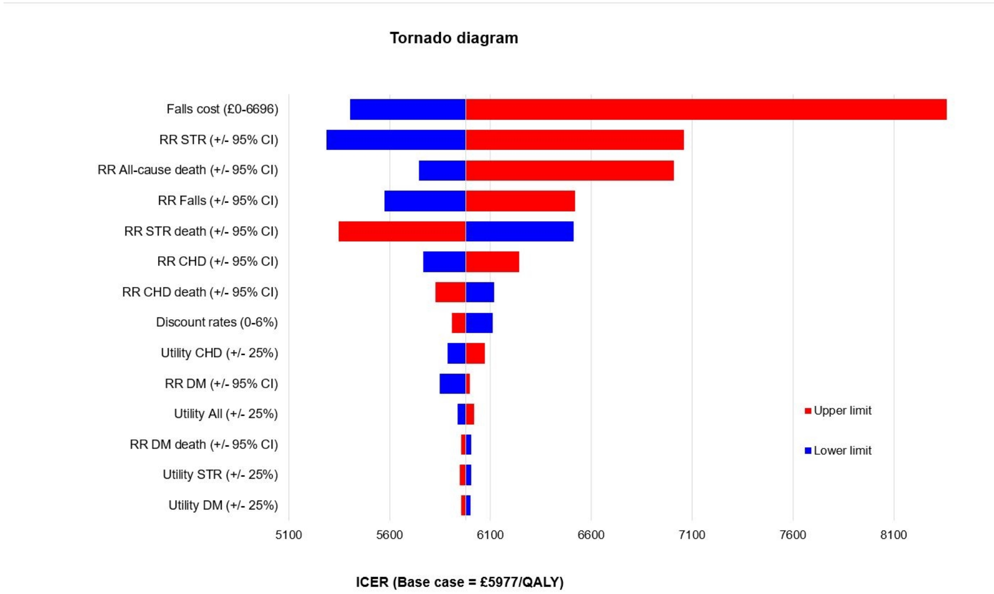
	Mean	Standard Error	Source
Coronary heart disease	0.648[a]	0.02	*Sullivan et al. 2011, ICD-9 414 (Web Table 5 + age decrement)*
Stroke	0.516	0.02	*Sullivan et al. 2011, ICD-9 436 (Web Table 5 + age decrement)*
Diabetes mellitus	0.656	0.006	*Sullivan et al. 2011, ICD-9 250 (Web Table 5 + age decrement)*
Healthy	0.818	0.008	*Sullivan et al. 2011, MEPS General mean EQ-5D score (Web Table 1 + age decrement)*
Age decrement	-0.00027	0.0002	*Sullivan et al. 2011, Age disutility covariate (Web Table 4)*

[a] CHD utility at age 80 (using age decrement) = 0.651357[ICD-9 414, age 67] + (-0.00027*13)



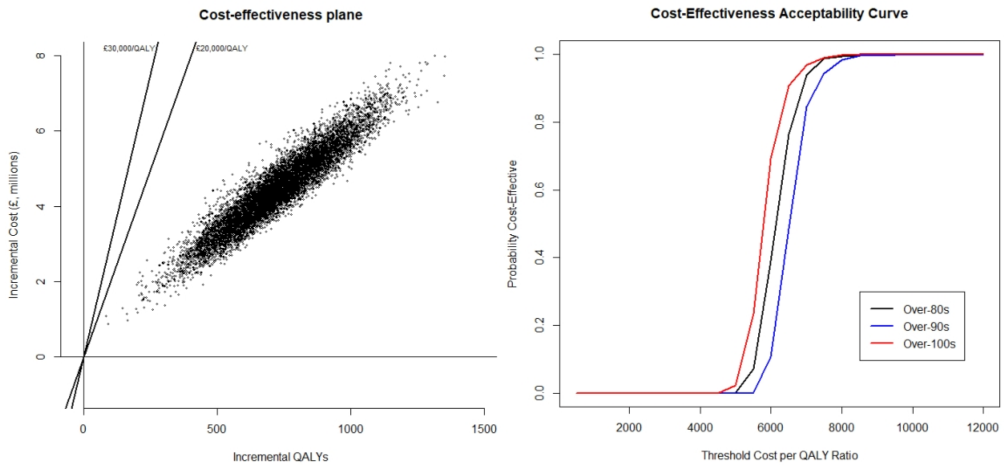
Schematic diagram of age-stratified Markov model. CHD, Coronary Heart Disease; STR, Stroke; DM, Diabetes Mellitus.

136x79mm (300 x 300 DPI)



Tornado diagram of univariate sensitivity analysis. RR, relative risk; STR, stroke; CHD, coronary heart disease; DM, diabetes mellitus.

118x73mm (300 x 300 DPI)



Cost-effectiveness plane and cost-effectiveness acceptability curve.

ABSTRACT

Background: Blood pressure and anti-hypertensive treatment generally increase with age but there is uncertainty concerning the value of treatment at very advanced ages.

Objectives: ~~This study aimed to~~To estimate ~~the~~ cost-effectiveness of anti-hypertensive treatment (AHT) in people aged 80 years and over.

Methods: A Markov model compared AHT with no blood pressure treatment for ~~the~~ prevention of cardiovascular disease. Outcomes were new stroke, coronary heart disease and diabetes, with falls included as a potential complication of AHT. Costs were evaluated from a health system perspective. Incidence, mortality and costs of health care utilisation were estimated from linked primary and secondary care electronic health records for 98,220 individuals aged 80 ~~years~~ and older. Clinical ~~trial~~ effectiveness estimates were from the Hypertension in the Very Elderly Trial (HYVET). Deterministic and probabilistic sensitivity analyses were conducted.

Results: In the base case, AHT ~~for all individuals aged 80 and over, compared with no treatment,~~ was associated with an additional 725 ~~incremental~~ quality adjusted life years (QALYs) and ~~incremental health care costs of~~ £4.3 million per 1000, with an incremental cost-effectiveness ratio (ICER) of £5977 per QALY. The ICER was most sensitive to the ~~estimated~~ cost of falls and ~~the~~ relative risk reduction in stroke incidence. Probabilistic sensitivity analysis gave 95% uncertainty intervals: ~~from~~ £5057~~5098~~ to £8398~~8582~~ per QALY in men and £4955~~4992~~ to £8218~~8255~~ per QALY in women. AHT for secondary prevention in participants with CHD gave an ICER of £9903~~9961~~ per QALY.

Conclusions: AHT is estimated to be cost-effective in individuals aged 80 years and over, even if health benefits are smaller or side effects costlier than in the base case. Benefits and harms for vulnerable sub-groups require further evaluation.

Highlights

What is already known about the topic?

- Blood pressure levels and treatment with anti-hypertensive therapy (AHT) increase with age but there is uncertainty concerning the value of treatment at very advanced ages beyond 80 years.

What does the paper add to existing knowledge?

- AHT in over-80s was associated with 725 incremental quality adjusted life years (QALYs) and incremental health care costs of £4.3 million per 1000, resulting in an incremental cost-effectiveness ratio (ICER) of £5977 per QALY. The ICER estimate was sensitive to the costs of treatment-associated falls but AHT was considered cost-effective in over-80s even if side effects are more costly than in the base case.

What insights does the paper provide for informing health care-related decision making?

- Treatment for hypertension over the age of 80 years is cost-effective after accounting for falls, with a high probability of health benefit at acceptable cost even under less favourable assumptions. These findings may contribute new information to inform guidelines for treating hypertension in over-80s.

INTRODUCTION

High blood pressure (BP), or clinical hypertension, is the most important risk factor for cardiovascular diseases (CVDs) including stroke, heart failure and myocardial infarction [1 2]. Blood pressure levels generally increase with age [3 4] and the prevalence of hypertension and treatment with antihypertensive therapy (AHT) is very high in older adults, despite uncertainties concerning the risks and benefits of treatment at advanced ages.[5 6] The occurrence of CVD has also shifted to older ages. CVDs now represent one of the most costly disease categories, with direct costs of $555 billion in the United States (US) in 2016 and £19 billion annually in the United Kingdom (UK).[7 8]

While many studies have provided evidence of the effectiveness of AHT for cardiovascular prevention in middle-aged adults, the evidence at older ages is less clear. Several studies have reported benefits of AHT in people over 60 years, particularly for prevention of stroke, [9-12] but potential benefits in people aged over 80 years are less well-established. The HYpertension in the Very Elderly Trial (HYVET) [13] is the only placebo-controlled trial to evaluate the effectiveness of AHT in participants aged 80 years or older. The HYVET trial provided evidence of reduction in stroke incidence and mortality, as well as lower all-cause mortality, with AHT. [13] Eligible participants in HYVET may have had less comorbidity than in a general population sample of older adults but the HYVET investigators found no evidence that the intervention effect depended on frailty level. [14] In the Systolic Blood Pressure Intervention Trial (SPRINT), which employed a treat-to-target BP strategy in participants aged 75 and over, AHT was associated with lower rates of CVD events and lower all-cause mortality, but intervention was associated with slightly higher rates of kidney injury and syncope.[15] Non-randomis~~z~~ed epidemiological studies report that comorbidity and frailty are frequent in this age-group, consequently adverse effects including orthostatic hypotension and falls assume greater importance at older ages.[5 16] Many authors emphasize the importance of considering adverse events, cautioning against aggressive BP-lowering in the very elderly.[17 18]

Guidelines for treating hypertension in older people are inconsistent. The American Heart Association (AHA) and American College of Cardiology (ACC) recently recommended that the threshold systolic blood pressure (SBP) level for initiating treatment in over-65s should be reduced from 140 mm Hg to 130 mm Hg. [19 20] In contrast, the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) recommend the SBP threshold of 150 mm Hg in over-60s [21], consistent with the National Institute for Care Excellence (NICE) recommendations in the UK for over-80s.[22] In the absence of sufficient evidence, it is uncertain which individuals should be classified as hypertensive and treated with AHT. Improved evidence on the cost-effectiveness of AHT in over-80s may help to inform this debate.

One previous health economic evaluation [23] was conducted in the age-group over 80 years, evaluating cost-effectiveness of AHT from a Swiss health care perspective. This Swiss study used life-years as its main health outcome and concluded that treatment was cost-effective. However, the data available for analysis suffered from several limitations. The study did not estimate quality adjusted life years as a preferred outcome; costs were extrapolated from studies in younger age-groups; and adverse events were not accounted for. The present study aimed to add to this limited evidence base, by estimating the cost-effectiveness of AHT in individuals aged 80 years and older. The study draws on empirical data from the UK through epidemiological analysis of electronic health records. These analyses provided population-based estimates for the probability of transitioning between each of the model's health states.

Analyses also provided empirical estimates for health care resource use. Potential adverse events from treatment were ~~also~~ accounted for in the model through the inclusion of falls.

METHODS

Intervention comparators

Cost-effectiveness of universal AHT, using a diuretic and an ACE-inhibitor if needed, was evaluated in comparison with no AHT. A population-wide strategy in which all individuals over 80 years are treated is justified by clinical guidelines, which generally recommend that treatment for hypertension should be based on individuals' overall 10-year CVD risk.[19 22 24-26] Increasing age is the strongest predictor of risk, with all individuals aged 80 years and older generally being classified at high-risk~~,~~; though not all existing risk scores are designed to be applicable at advanced ages.[27]

Model structure

A Markov model was designed including five health states: 'At risk', 'Coronary Heart Disease' (CHD), 'Stroke' (STR), 'Type 2 Diabetes Mellitus' (DM) and 'Dead'. Each state was further subdivided by single year of age and gender (Figure 1). Falls associated with AHT were accounted for in each cycle of the model as a potential adverse event in very elderly populations.

Patient population and subgroup analyses

The base-case modelled population was gender stratified (35% males and 65% females) according to the composition of the over-80 CPRD population and the United Nations World Population Ageing estimates.[28] Subgroup analyses were conducted by varying the starting age and gender distribution in the model. The cost-effectiveness of AHT for secondary prevention was evaluated in a start population with CHD.

Data sources

Data used to populate the model were derived from epidemiological analysis of primary care electronic health records data from a cohort of participants registered with the UK's Clinical Practice Research Datalink (CPRD). The CPRD is a nationally representative sample of approximately 680 primary care practices across the UK. Health care utilisation and costs, including prescriptions, were estimated for each health state from CPRD electronic health records, with linked secondary care Hospital Episode Statistics (HES) data. [29 30] A systematic review was conducted to obtain data for treatment effectiveness in the model.

Epidemiological and costing analyses

Age-specific estimates of incidence, mortality and costs for each health state were estimated from a cohort of 98,220 participants aged 80 years and older drawn from analysis of electronic health records with linked hospital episodes data. [30 31] These analyses provided empirical estimates to underpin the model that are broadly representative of the UK's over-80 population, including representation of frail and multi-morbid individuals. The study cohort provided 200,719 person-years for epidemiological and costing analysis at 80-89 years, 95,431 person-years at 90-99 years, and 4,544 person-years at 100 years and older. Rates of incidence and mortality were estimated in a time-to-event framework using a Weibull survival model, providing transition probabilities for movement between health states in the Markov model (Supplementary Table 1). Variance estimates from the Weibull model were also be incorporated into a probabilistic sensitivity analysis (PSA) to assess uncertainty in the model. Survival analyses were completed using CPRD data from 2001-14.

Costs were estimated based on utilisation of primary care services in CPRD (general practice consultations, telephone consultations, home visits, emergency and out-of-hours consultations) and secondary care services in hospital episodes statistics (inpatient hospital admissions, outpatient visits, day case visits and emergency admissions), including prescriptions (Supplementary Table ~~1~~2). Unit costs were derived from the NHS reference costs and the Personal Social Services Research Unit (PSSRU). A two-part regression model was employed, as reported previously [30], to determine mean annual costs for each health state, stratified by age. Falls costs were ~~also similarly~~ estimated similarly through epidemiological analysis of falls incidence and costs of falls in CPRD and HES, including all costs associated with a fall in a given year. This includes health care costs associated with any potential fractures following a fall.

Intervention effects and unit costs

Clinical effectiveness measures for over-80s were drawn from the HYVET trial (Supplementary Table ~~2~~3). Treatment was associated with a 30% relative risk (RR) reduction in the rate of stroke (RR = 0.70, 95% CI: 0.49 to 1.01), a 39% reduction in the rate of stroke mortality (RR = 0.61, 95% CI: 0.38 to 0.99), a 34% reduction in CHD (RR = 0.66, 95% CI: 0.53 to 0.82), and a 21% reduction (RR = 0.79, 95% CI: 0.65 to 0.95) in all-cause mortality.[32 33] It was assumed that any improvement in diabetes mortality was equivalent to the improvement in all-cause mortality, as these data for over-80s were not available. Based on systematic review evidence, we assumed no effect of AHT on diabetes incidence in the base-case analysis, but a 19% reduction (RR=0.81, 95% CI 0.62 to 1.06) in diabetes incidence [34] was employed in a sensitivity analysis from a sample aged greater than~~≥~~ 65 years, in the absence of any data for over-80s.

The relative incidence of experiencing a fall, between treated and not treated individuals, was applied to the model based on a non-randomised epidemiological study by Tinetti et al.[16] in the absence of trial data. Based on Tinetti et al., AHT was associated with a 40% relative increase in falls (RR = 1.40, 95% CI: 1.03 to 1.90) among a nationally representative sample of adults aged 70 years and older in the US, providing a conservative estimate for the model.

Intervention costs of treatment with AHT were estimated at £51.87 per year using the British National Formulary and the CPRD drug dictionary, based on the drugs used in HYVET. Unit costs of primary care consultations were: GP consultation, £45; telephone consultation, £27; home consultation, £88.92; out-of-hours consultation, £45 [35]. Secondary care consultations included: day case, £721; inpatient, £2729.64; outpatient, £275; accident & emergency, £132.[36]

Time horizon and discounting

All outcomes were modelled using a lifetime horizon with a one-year cycle length. Both costs and health outcomes were discounted at an annual rate of 3.5% [37].

Model outcomes

Health outcomes were valued using quality-adjusted life-years (QALYs) and utility values used to calculate QALYs were drawn from data published in a compendium of EuroQol five-dimensional (EQ-5D) questionnaire utility values for the UK participants by health condition and age (Supplementary Table 4) [38]. Costs (£, GBP) are presented from a health system perspective, adopting any health care, medical care and drug costs borne by the UK National Health Service.

Sensitivity analysis

To characterise uncertainty, a univariate sensitivity analysis was conducted to assess the individual impact of changes in input parameters on the resulting ICER [39]. Values were varied primarily based on 95% confidence intervals for parameter estimates. An alternative cost for falls was employed using a previously published estimate of cost in the 12 months following a fall [40], assuming that most excess costs would occur in the year after a fall.

A probabilistic sensitivity analysis was also conducted by applying distributional assumptions to each parameter, representing statistical uncertainty across all model inputs simultaneously, and randomly selecting values across 10,000 simulations. Annual transition probabilities for the model were obtained by sampling from normal distributions using EHR-derived estimates as inputs. Beta distributions were employed for utility data and gamma distributions for cost data [41]. Relative risks were sampled using a lognormal distribution.

Model validation

Model validation comprised face validity (setting parameters to extreme values to assess predictable effects on outputs), internal validity (consistency of results across software platforms, Excel and R) and external validity (review by external experts). The base case model was built in both Excel and R, while the probabilistic sensitivity analyses was run in R for improved computational time.

Ethics

The use of fully anonymized CPRD data was approved by the Medicines and Healthcare products Regulatory Agency's Independent Scientific Advisory Committee (Protocol number 15_047).

RESULTS

In the base case, the model start population comprised 1,000 individuals aged 80 years without long-term conditions, including 650 women and 350 men. AHT was associated with an overall increase of 725 QALYs per 1000 individuals entering the model, compared to no treatment, with 7,025 lifetime QALYs per 1000 (4,731 for females, 2,294 for males) in the treatment group and 6,300 lifetime QALYs per 1000 (4,256 for females, 2,044 for males) in the control group (Table 1). AHT was associated with an increased cost of £4.3 million per 1000 individuals compared to no treatment, with costs equating to £32.4 million per 1000 in the treatment group (£21.2 million for females, £11.2 million for males) and £28.1 million in the control group (£18.4 million for females, £9.7 million for males). The cost of falls amounted to £1.1 million per 1000 in the treatment group and £684,542 per 1000 in the control group, indicating higher falls cost in those taking AHT compared to those not on AHT. AHT, in comparison with no treatment, was associated with a decrease in the number of life-years lived with CHD and stroke, but an increase in the number of years lived with diabetes resulting from longer duration survival with AHT. The additional lifetime health care costs per 1000 associated with an increase of 23.6 person years lived with diabetes were £125,482 (£750,522 in the treatment arm and £625,040 in the control arm).

For an 80-year old individual, the additional lifetime cost of anti-hypertensive treatment was £4,334~~00~~ for an additional 0.725 QALYs gained. The estimated incremental cost-effectiveness ratio (ICER) (lifetime cost per QALY) for AHT in the base-case was £5,977 per

QALY (Table 1). Considering the UK's willingness-to-pay (WTP) threshold range of £20,000-30,000 per QALY, AHT can be considered cost-effective in over-80s even after accounting for the costs of adverse events through falls. While treatment appeared to be slightly less cost-effective for males than females, the ICERs for both were still well below the UK's threshold range (£5,910 per QALY in females; £6,105 per QALY in males). If the WTP threshold were £30,000 per QALY, the net monetary benefit (NMB) to the health service associated with AHT in over-80s is valued at approximately £17.4 million per 1000 individuals, or £10.2 million if each QALY gained is valued at £20,000 (Table 1).

Characterising uncertainty

In a one-way sensitivity analysis, cost-effectiveness was most sensitive to changes in the cost of falls (Figure 2). Despite varying this most influential parameter in the model, the ICER remained below the threshold range for cost-effectiveness. Increasing the annual falls cost from £1,300 in the base case to £6,696 in the deterministic sensitivity analysis resulted in an increased ICER of £8,364 per QALY. The relative risk reduction for stroke was also an influential model parameter. When varying this value to indicate a smaller difference in stroke rates between groups, the ICER increased to £7,058 per QALY, also remaining cost-effective. With a lower limit of 0.49, indicating a greater stroke reduction with treatment, the ICER decreased to £5,287 per QALY. Changes in the discount rate and utility values had minimal effect on cost-effectiveness, as the ICER remained between £5,887 and £6,111 per QALY with variations in these parameters. Sensitivity of the ICER to selected input parameters is summarised in Figure 2.

Probabilistic sensitivity and subgroup analysis

The base-case probabilistic model for over-80s yielded an ICER of £6,~~176~~ 146 per QALY (95% uncertainty interval (UI) £5,~~350~~ 291 to £7,~~532~~446), and subgroup analysis indicated slightly greater cost-effectiveness in females (£6,~~096~~ 074 per QALY, 95% UI £4,~~992~~ 955 to £8,218~~55~~) compared to males (£6,~~328~~ 281 per QALY, 95% UI £5,~~098~~ 057 to £8,~~582~~398) (Table ~~3~~2). Uncertainty intervals represent the 95% range for estimates from all simulations. Incremental differences in costs and QALYs between comparator groups for 10,000 simulations are presented in a cost-effectiveness plane (Figure 3, left panel). With all points falling below the £30,000 per QALY and £20,000 per QALY thresholds, treatment remained cost-effective after accounting for distributional uncertainty in all model parameters.

When evaluating older age sub-groups, the ICER remained below the threshold for cost-effectiveness, at £6,~~526~~ 521 per QALY in over-90s and £5,759 per QALY in over-100s. Treatment was most cost-effective in centenarians overall (95% UI £5,~~013~~ 025 to £7,~~155~~071). AHT was more cost-effective for females over 80 and 90 years, but cost-effectiveness was greater for males over 100 years.

AHT for secondary prevention of CVDs was less cost-effective compared to primary prevention, with an ICER of £9,903~~892~~ per QALY (95% UI £9,~~368~~ 364 to £12,~~294~~322) in over-80s and £11,~~103~~ 102 ~~($14,989)~~ per QALY in over-90s. While primary prevention with AHT was more cost-effective than treatment for secondary prevention, both can be considered cost-effective options based on the UK's threshold range. Age-specific cost-effectiveness acceptability curves summarise uncertainty in the estimates of cost-effectiveness by age (Figure 3, right panel). AHT proved to be cost-effective in all age-groups 100% of the time, with the probability of being cost-effective equal to 1.00 (over-80s and over-100s) or 0.999 (over-90s) at a WTP threshold of £30,000 per QALY.

DISCUSSION

This research drew on empirical electronic health records data to model the cost-effectiveness of AHT in individuals aged 80 years and older. The study incorporated several novel aspects. This is the first study in this age-group to incorporate quality of life by using QALYs as an outcome measure to evaluate cost-effectiveness of AHT. The only other existing economic evaluation of AHT in over-80s used life years as its main health outcome in a Swiss context.[23] Our model is also the first of its kind to account for falls as a potential adverse event in the evaluation of cost-effectiveness, a significant concern and cost driver in the very elderly. Increased QALYs associated with treatment resulted from lower incidence of CHD and stroke and reduced cardiovascular mortality. Higher costs in the treatment group arose primarily from increased longevity associated with AHT, but also from increased falls costs captured as an adverse consequence of treatment at advanced ages.

AHT was highly cost-effective in this older age-group aged 80 years and over, even after accounting for uncertainty in all model parameters. This conclusion should be cautiously limited to relatively fit over-80s, as our estimates for treatment effectiveness originate from HYVET participants with few comorbidities and low levels of frailty. Treatment was more cost-effective in centenarian men compared to women, likely because they incur less incremental cost increase from treatment as a result of being typically healthier with less chronic morbidity compared to female centenarians.[42-44]

Cost-effectiveness was most sensitive to the relative risk for stroke and all-cause mortality estimates, and the cost of falls. Falls costs are difficult to measure at a population level because falls have wide ranging spectrums of severity and subsequent treatment or follow-up after an event can vary greatly. This will depend on the nature and scale of the fall (e.g.

impact on hip, head, femur, wrist) and the health status of the older individual experiencing the fall such as whether they experience multi-morbidity or polypharmacy. Despite the importance of falls in older populations, the cost of falls has not previously been incorporated in economic models evaluating the cost-effectiveness of AHT in the elderly, potentially indicating the scarcity of available data for this parameter.

Strengths and limitations

While economic evaluations are a widely used method to make trade-offs between costs and outcomes more explicit, these studies are scarce in over-80s for all treatment areas as there are less representative epidemiological data to inform estimates specific to this age-group. Findings from this study hold the strengths of using population-based nationally representative epidemiological data from a severely understudied elderly age-group. This allowed for empirical estimates to underpin the model that are broadly representative of the UK's over-80 population, including partial representation of frail and multi-morbid individuals.

The study is limited mostly by a scarcity of effectiveness and utility ~~and effectiveness~~ data specific to the general population of individuals over 80. Only one placebo-controlled trial has been conducted in this age-group, and mean utilities were attained for younger ages with an age decrement applied to extrapolate age-specific utilities beyond 80 years of age. Using this decrement approach for utilities may represent a limitation, as later years of life may not always correspond to decreases in quality of life, as we reported previously.[31 44] ~~.~~ This was however accounted for in sensitivity analyses where this age decrement was only applied up to 95 years, and did not have a large impact on the ICER. We did not assume a utility decrement associated with falls because of the high variability in falls outcomes. In addition, there was no available falls disutility in the literature based on a generic preference-based measure that would consider all possible clinical outcomes. This approach is consistent with a previous cost-effectiveness model of bariatric surgery, where the cost of complications but not disutility associated with the complications were included because of a lack of data.[45]

This model did not include comorbidity health states, but this will be partially accounted for in the underlying population-based estimates of the model where existing comorbidities will be equally impactful in both groups. While we included the impact of falls incidence, we did not model any possible impact on renal function. Blood pressure lowering may sometimes contribute to renal insufficiency but AHT is also expected to reduce age-related decline in renal function. As with most economic evaluations, our model represented a simplification of the clinical reality. There are benefits from opting for less complex health economic models, to minimise the inevitable uncertainty based on data inputs.

Given the estimates of treatment effect that underpin our model originate from HYVET, there are concerns regarding the generalisability of this evidence from a carefully selected group of older participants. Participants from HYVET were subject to several exclusions and are likely to be healthier than the general elderly hypertensive population. Hypertension treatment at the advanced age of 80 and older is often delivered in the context of frailty, multiple morbidity and polypharmacy and these vulnerable individuals are not fully represented in the trial data. Data from HYVET were used for all individuals in the model up to 100 years and over. ~~HYVET~~ We acknowledge that only 4.6% of HYVET patients were aged 90 years or over, but this trial currently~~still~~ provides the best available ~~treatment~~ effectiveness data ~~from a randomised placebo-controlled trial in this age-group~~ for modelling the cost-effectiveness of AHT;~~.~~ trial effectiveness data are not presently available for centenarians as a sub-group.

All other estimates underpinning the model were obtained from a representative population-based sample of over-80s, offering age-specific values of incidence and mortality rates up to 100 years and over, as well as age-specific costs, -potentially offsetting these generalisability concerns. Additional sensitivity analysis also allowed for a wide range of uncertainty estimates.

Conclusions and what this study adds

Despite the importance of potential harms from medicines in over-80s, previous economic evaluations on AHT in this age-group have not incorporated adverse events, likely due to scarcity of data. This model acknowledges the additional costs of potential side effects from AHT use in the elderly, which may often result in falls from syncope, orthostatic hypotension and dizziness.

Our model adds to the limited existing literature by, firstly, using population-based UK estimates, secondly, accounting for adverse events through falls and, thirdly, using quality of life data allowing for QALYs to be used as the main health outcome measure in the model. The use of QALYs in our model allows decision makers to compare our findings with results from other clinical areas to make health care coverage decisions across a range of clinical areas. This study also demonstrates the cost-effectiveness of taking a population-based approach to condition management with age being the first indicator of treatment followed by decision-making around frailty rather than a more elaborate risk assessment process.

Improved evidence concerning possible adverse outcomes of AHT in vulnerable older sub-groups is still needed. As frailty levels increase, there may be more adverse events, fewer life expectancy gains, and lower incremental costs of AHT. There remains a need to estimate effectiveness of AHT at different levels of frailty before determining cost-effectiveness in more vulnerable sub-groups of older people.

REFERENCES

1. Forouzanfar MH, Alexander L, Anderson HR, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386(10010):2287-323. doi: 10.1016/s0140-6736(15)00128-2 [published Online First: 2015/09/15]
2. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/s0140-6736(12)61689-4 [published Online First: 2012/12/19]
3. Pinto E. Blood pressure and ageing. *Postgrad Med J* 2007;83(976):109-14. doi: 10.1136/pgmj.2006.048371
4. Zhao Y, Yan H, Marshall RJ, et al. Trends in population blood pressure and prevalence, awareness, treatment, and control of hypertension among middle-aged and older adults in a rural area of Northwest China from 1982 to 2010. *PloS one* 2013;8(4):e61779. doi: 10.1371/journal.pone.0061779 [published Online First: 2013/04/25]
5. Benetos A, Rossignol P, Cherubini A, et al. Polypharmacy in the Aging Patient: Management of Hypertension in Octogenarians. *JAMA* 2015;314(2):170-80. doi: 10.1001/jama.2015.7517 [published Online First: 2015/07/15]
6. Stott DJ, Applegate WB. Perspectives on hypertension treatment in older persons. *Age Ageing* 2018:afy055. doi: 10.1093/ageing/afy055
7. American Heart Association. Cardiovascular disease: a costly burden for America - projections through 2035, 2017.
8. British Heart Foundation. Cardiovascular Disease Statistics: BHF UK Factsheet, 2018.
9. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991;265(24):3255-64. [published Online First: 1991/06/26]
10. Amery A, Brixko R, Clement D, et al. Efficacy of antihypertensive drug treatment according to age, sex, blood pressure, and previous cardiovascular disease in patients over the age of 60. *Lancet* 1986;328(8507):589-92. doi: https://doi.org/10.1016/S0140-6736(86)92424-4
11. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350(9080):757-64. doi: https://doi.org/10.1016/S0140-6736(97)05381-6
12. Musini VM, Tejani AM, Bassett K, et al. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev* 2009(4):CD000028. doi: 10.1002/14651858.CD000028.pub2 [published Online First: 2009/10/13]
13. Beckett NS, Peters R, Fletcher AE, et al. Treatment of Hypertension in Patients 80 Years of Age or Older. *N Engl J Med* 2008;358(18):1887-98. doi: 10.1056/NEJMoa0801369
14. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC medicine* 2015;13:78. doi: 10.1186/s12916-015-0328-1 [published Online First: 2015/04/17]

15. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. *Jama* 2016;315(24):2673-82. doi: 10.1001/jama.2016.7050 [published Online First: 2016/05/20]
16. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine* 2014;174(4):588-95. doi: 10.1001/jamainternmed.2013.14764
17. Conroy SP, Westendorp RGJ, Witham MD. Hypertension treatment for older people-navigating between Scylla and Charybdis. *Age Ageing* 2018 doi: 10.1093/ageing/afy053 [published Online First: 2018/05/23]
18. Wilt TJ, Kansagara D, Qaseem A. Hypertension Limbo: Balancing Benefits, Harms, and Patient Preferences Before We Lower the Bar on Blood Pressure. *Annals of internal medicine* 2018;168(5):369-70. doi: 10.7326/m17-3293 [published Online First: 2018/01/23]
19. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *J Am Coll Cardiol* 2018;71(19):e127.
20. Krumholz HM. Blood pressure guidelines as starting point in clinical decisions. *BMJ* 2018;360
21. Qaseem A, Wilt TJ, Rich R, et al. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: A clinical practice guideline from the american college of physicians and the american academy of family physicians. *Annals of internal medicine* 2017;166(6):430-37. doi: 10.7326/M16-1785
22. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management [CG127], 2016.
23. Szucs TD, Waeber B, Tomonaga Y. Cost-effectiveness of antihypertensive treatment in patients 80 years of age or older in Switzerland: an analysis of the HYVET study from a Swiss perspective. *J Hum Hypertens* 2010;24(2):117-23. doi: 10.1038/jhh.2009.47
24. British Hypertension Society. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;328(7445):926. doi: https://doi.org/10.1136/bmj.328.7445.926
25. Williams B, Poulter NR, Brown MJ, et al. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;328(7440):634-40.
26. Fuster V, Gambús F, Patriciello A, et al. The polypill approach – An innovative strategy to improve cardiovascular health in Europe. *BMC Pharmacol Toxicol* 2017;18:10. doi: 10.1186/s40360-016-0102-9
27. Carlson E, Kipps M, Thomson J. Influences on the food habits of some ethnic minorities in the United Kingdom. *HumNutrApplNutr* 1984;38(2):85-98.
28. United Nations. World Population Ageing 1950-2050: Population Division, DESA, United Nations, 2002.
29. Gulliford MC, Charlton J, Prevost T, et al. Costs and Outcomes of Increasing Access to Bariatric Surgery: Cohort Study and Cost-Effectiveness Analysis Using Electronic Health Records. *Value in Health* 2017 doi: 10.1016/j.jval.2016.08.734
30. Hazra NC, Rudisill C, Gulliford MC. Determinants of health care costs in the senior elderly: age, comorbidity, impairment, or proximity to death? *The European Journal of Health Economics* 2017 doi: 10.1007/s10198-017-0926-2

31. Hazra NC, Gulliford MC. Evolution of the "fourth stage" of epidemiologic transition in people aged 80 years and over: population-based cohort study using electronic health records. *Popul Health Metr* 2017;15(1):18. doi: 10.1186/s12963-017-0136-2
32. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *New Engl J Med* 2008;358(18):1887-98. doi: http://dx.doi.org/10.1056/NEJMoa0801369
33. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *J Hypertens* 2010;28(7):1366-72. doi: http://dx.doi.org/10.1097/HJH.0b013e328339f9c5
34. Padwal R, Mamdani M, Alter DA, et al. Antihypertensive Therapy and Incidence of Type 2 Diabetes in an Elderly Cohort. *Diabetes Care* 2004;27(10):2458-63.
35. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2015. Kent: The University of Kent, 2015.
36. Department of Health. National schedule of reference costs: the main schedule, 2014-15, 2015.
37. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013, 2013.
38. Sullivan PW, Slejko JF, Sculpher MJ, et al. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making* 2011;31(6):800-4. doi: 10.1177/0272989x11401031 [published Online First: 2011/03/23]
39. York Health Economics Consortium. Univariate/One Way Sensitivity Analysis York2016. [Available from: http://www.yhec.co.uk/glossary/univariateone-way-sensitivity-analysis/ accessed Oct 24 2017.]
40. The King's Fund. Exploring the system-wide costs of falls in older people in Torbay, 2013.
41. Gray A, Clarke PM, Wolstenholme JL, et al. Applied Methods of Cost-effectiveness Analysis in Healthcare. New York, NY: Oxford University Press 2010.
42. Evert J, Lawler E, Bogan H, et al. Morbidity Profiles of Centenarians: Survivors, Delayers, and Escapers. *J Gerontol A* 2003;58(3):M232-M37. doi: 10.1093/gerona/58.3.M232
43. Franceschi C, Motta L, Valensin S, et al. Do men and women follow different trajectories to reach extreme longevity? Italian Multicenter Study on Centenarians (IMUSCE). *Aging (Milan, Italy)* 2000;12(2):77-84. [published Online First: 2000/07/21]
44. Hazra NC, Dregan A, Jackson S, et al. Differences in Health at Age 100 According to Sex: Population-Based Cohort Study of Centenarians Using Electronic Health Records. *J Am Geriatr Soc* 2015;63(7):1331-37. doi: http://dx.doi.org/10.1111/jgs.13484
45. Gulliford MC, Charlton J, Prevost T, et al. Costs and Outcomes of Increasing Access to Bariatric Surgery: Cohort Study and Cost-Effectiveness Analysis Using Electronic Health Records. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2017;20(1):85-92. doi: 10.1016/j.jval.2016.08.734 [published Online First: 2017/02/19]

Table 1: Results from base-case deterministic model per thousand persons.

	Treatment	No Treatment	Incremental
Total discounted costs			
Overall	£32,447,727	£28,113,532	£4,334,196
Females	£21,224,916	£18,413,859	£2,811,057
Males	£11,222,812	£9,699,673	£1,523,139
Total discounted QALYs			
Overall	7,025	6,300	725
Females	4,731	4,256	476
Males	2,294	2,044	249
Incremental Cost-Effectiveness Ratio			
Overall		£5,977 per QALY	
Females		£5,910 per QALY	
Males		£6,105 per QALY	
WTP threshold	**Net Monetary Benefit (per 1,000 treated)**		**Net Health Benefit (per 1,000 treated)**
£30,000 per QALY	£17,415,804		580.5 QALYs
£20,000 per QALY	£10,165,804		508.3 QALYs

WTP = willingness to pay

Table 2: Incremental cost-effectiveness ratios (UK £ per QALY) and 95% uncertainty intervals from subgroup and probabilistic sensitivity analysis

	Incremental cost-effectiveness ratio (95% uncertainty interval, UK£ per QALY)		
	80 years and over	**90 years and over**	**100 years and over**
Base-case model			
Overall	6,146~~6,176~~ (~~5,350~~5,291 to 7,446~~7,532~~)	6,~~526~~ 521 (5,772~~99~~ to 7,829~~7844~~)	5,759 (~~5,013~~ 5,025 to ~~7,155~~7,071)
Females only	~~6,096~~6,074 (~~4,992~~4,955 to ~~8,255~~8,218)	6,410~~02~~ (5,417~~383~~ to 8,605~~556~~)	5,880~~8~~ (4,846~~00~~ to 8,509~~846~~)
Males only	~~6,328~~6,281 (~~5,098~~5,057 to ~~8,582~~8,398)	6,736~~61~~ (5,672~~64~~ to 8,678~~815~~)	5,557~~5,546~~ (4,681~~4,691~~ to 7,600~~7,174~~)
Secondary prevention			
Overall	~~9,892~~9,903 (9,364~~9368~~ to 12,322~~12,294~~)	11,102~~3~~ (10,503~~11~~ to 13,421~~6~~)	11,~~023~~ 003 (10,396~~70~~ to 13,167~~688~~)
Females	~~9,716~~9,727 (~~9006~~8,960 to 14,459~~16,239~~)	10,846~~9~~ (8,816~~855~~ to 154,466~~306~~)	10,~~907~~ 876 (~~6430~~ 9,874 to 15,297~~44~~)
Males	10,244~~10,235~~ (9,599~~6852~~ to 14,130~~13,334~~)	11,598~~608~~ (9,492~~10,991~~ to 154,~~789~~171)	11,231~~23~~ (10,316~~432~~ to 14,506~~283~~)

Legend for Figure 1: Schematic diagram of age-stratified Markov model. CHD, Coronary Heart Disease; STR, Stroke; DM, Diabetes Mellitus.

Legend for Figure 2: Tornado diagram of univariate sensitivity analysis. RR, relative risk; STR, stroke; CHD, coronary heart disease; DM, diabetes mellitus.

Legend for Figure 3: Cost-effectiveness plane and cost-effectiveness acceptability curve.

Supplementary Table 1: Survival models (incidence and mortality) for age- and gender-specific transition probabilities using CPRD data

Transition	Regression model[a]
Healthy to CHD	$y = -18.4 - 0.36x + 0.33z - 0.002z^2$
Healthy to STR	$y = -7.3 - 0.11x + 0.03z$
Healthy to DM	$y = -43.8 - 0.22x + 1.1z - 0.008z^2$
Healthy to Dead	$y = -11.3 - 0.28x + 0.10z$
CHD to Dead	$y = 1.61 - 0.29x - 0.16z + 0.001z^2$
STR to Dead	$y = -6.44 - 0.13x + 0.06z$
DM to Dead	$y = 23.75 - 0.29x - 0.73z + 0.005z^2$

[a] x = Gender (female = 2, male = 1); z = Age

Supplementary Table 2: Costs (UK £) of health care utilisation (including prescriptions) for Markov model from CPRD

	Females (mean)	Males (mean)
Healthy		
80-84	2815	3123
85-89	3502	3884
90-94	4051	4460
95-99	4488	4891
100+	3705	3754
Coronary Heart Disease		
80-84	4085	4635
85-89	5032	5702
90-94	5807	6509
95-99	6516	7254
100+	6179	6609
Stroke		
80-84	4433	5150
85-89	5419	6316
90-94	6222	7114
95-99	6940	7798
100+	6521	6993
Diabetes Mellitus		
80-84	3818	4487
85-89	4783	5567
90-94	5539	6427
95-99	6288	7071
100+	6898	5896
Falls		
All ages		1299.70

Supplementary Table 3: Intervention effects for Markov model

Condition	Mean Relative Risk (RR)	95% CI	Source
Incidence			
Coronary heart disease	0.66	0.53 to 0.82	*Beckett et al. 2008 (HYVET Main Trial)*
Stroke	0.70	0.49 to 1.01	*Beckett et al. 2008 (HYVET Main Trial)*
Diabetes mellitus	1.00	1.00 to 1.00	*N/A*
Falls	1.40	1.03 to 1.90	*Tinetti et al. 2014*
Mortality			
Coronary heart disease	0.77	0.60 to 1.01	*Beckett et al. 2008 (HYVET Main Trial)*
Stroke	0.61	0.38 to 0.99	
Diabetes mellitus	0.79	0.65 to 0.95	
All cause death	0.79	0.65 to 0.95	

Supplementary Table 4: Utility values for health states used in the model

	Mean	Standard Error	Source
Coronary heart disease	0.648[a]	0.02	*Sullivan et al. 2011, ICD-9 414 (Web Table 5 + age decrement)*
Stroke	0.516	0.02	*Sullivan et al. 2011, ICD-9 436 (Web Table 5 + age decrement)*
Diabetes mellitus	0.656	0.006	*Sullivan et al. 2011, ICD-9 250 (Web Table 5 + age decrement)*
Healthy	0.818	0.008	*Sullivan et al. 2011, MEPS General mean EQ-5D score (Web Table 1 + age decrement)*
Age decrement	-0.00027	0.0002	*Sullivan et al. 2011, Age disutility covariate (Web Table 4)*

[a] CHD utility at age 80 (using age decrement) = 0.651357[ICD-9 414, age 67] + (-0.00027*13)

Reviewer: 1

The authors performed a cost-utility analysis of anti-hypertensive treatment for the elderly. In general, the paper is well-written and tackles an interesting topic, while most RCTs target a relatively young population, the drugs are prescribed in much older patients in practice. Assessing the cost-effectiveness for this older population is valuable and should be done more often.

Although the model seems well-designed, this is not easily checked, as key parameters are missing from the manuscript, such as the transition probabilities. Please include a comprehensive table with all key model parameters included. Additionally, the supplementary tables are not included with this proof, likely containing further model parameters.

Response: Thank you for taking the time to review our paper. We have now included all key parameters in the supplementary tables, including survival models for calculating age- and gender-specific transition probabilities. Costs, utilities and relative risk estimates are also provided.

The patients included in the HYVET trial were primarily aged 80-90. It is unclear to me how these data were adapted to include a population aged 100 and over. In general, the question arises whether centennials should start with antihypertensive treatment in the first place, for which clinical evidence is lacking.

Response: Thank you for highlighting this. We have added to the Limitations section in the Discussion (page 15, paragraph 3): "Data from HYVET were used for all individuals in the model up to 100 years and over. We acknowledge that only 4.6% of HYVET patients were aged 90 years or over but this trial currently provides the best available effectiveness data for modelling the cost-effectiveness of AHT; trial effectiveness data are not presently available for centenarians as a sub-group. All other estimates underpinning the model were obtained from a representative population-based sample of over-80s, offering age-specific values of incidence and mortality rates up to 100 years and over, as well as age-specific costs, potentially offsetting these generalisability concerns."

Minor comments:

While it is commendable that falls have been included as an adverse effect, the long-term complications of a potential fracture following a fall, may have a large impact on the model, as the model is very sensitive to the costs associated with falls.

Response: Thank you for raising this important point. We used a two-part model to determine a mean annual cost for those who experienced a fall. This includes all health care costs associated with a fall, including any potential fractures following a fall. We have added to the Methods section (page 7, paragraph 1): “Falls costs were estimated similarly through epidemiological analysis of falls incidence and cost of falls in CPRD and HES, including all costs associated with a fall in a given year. This includes health care costs associated with any potential fractures following a fall.”

Additionally, I am quite interested in the utility decrement for falls.

Response: We agree, this is a very good point. A section has been added to the Limitations section discussing this (page 14, paragraph 3): “We did not assume a utility decrement associated with falls because of the high variability in falls outcomes. In addition, there was no available falls disutility in the literature based on a generic preference-based measure that would consider all possible clinical outcomes. This approach is consistent with a previous cost-effectiveness model of bariatric surgery, where the cost of complications but not disutility associated with the complications were included because of a lack of data.”

1,000 Monte Carlo simulations have been included for the probabilistic sensitivity analysis, while currently 10,000 seems more common. Please elaborate on the choice to include 1,000.

Response: Thank you for this comment. We have now run the probabilistic sensitivity analysis using 10,000 Monte Carlo simulations. The cost-effectiveness plane and cost-effectiveness acceptability curves in Figure 3, as well as the PSA results in Table 2 and in the text, have been updated accordingly.

Parts of the model are built using Excel and parts using R, please explain what is used for what.

Response: The deterministic model was built in Excel and this was replicated in R, providing one of three forms of validation. The probabilistic sensitivity analyses was run only in R as this was a more efficient computing environment for running Monte Carlo simulations. A sentence has been added to the Methods under the Model Validation section (page 9, paragraph 3): “The base case model was built in both Excel and R, while the probabilistic sensitivity analyses was run in R for improved computational time.”

One of the results of the model is the increase in years lived with diabetes, what are the costs associated with this increase?

Response: We have now added a sentence to the results outlining the costs associated with the increase in life years lived with diabetes (page 10, paragraph 2): "The additional lifetime health care costs per 1000 associated with an increase of 23.6 person years lived with diabetes were £125,482 (£750,522 in the treatment arm and £625,040 in the control arm)."

It would be nice to add a £20,000 threshold to Figure 3.

Response: Thank you for this suggestion. We have now added a £20,000 per QALY threshold to the cost-effectiveness plane in Figure 3.

Supplementary Table 1: Survival models (incidence and mortality) for age- and gender-specific transition probabilities using CPRD data

Transition	Regression model[a]
Healthy to CHD	$y = -18.4 - 0.36x + 0.33z - 0.002z^2$
Healthy to STR	$y = -7.3 - 0.11x + 0.03z$
Healthy to DM	$y = -43.8 - 0.22x + 1.1z - 0.008z^2$
Healthy to Dead	$y = -11.3 - 0.28x + 0.10z$
CHD to Dead	$y = 1.61 - 0.29x - 0.16z + 0.001z^2$
STR to Dead	$y = -6.44 - 0.13x + 0.06z$
DM to Dead	$y = 23.75 - 0.29x - 0.73z + 0.005z^2$

[a] x = Gender (female = 2, male = 1); z = Age

Supplementary Table 2: Costs (UK £) of health care utilisation (including prescriptions) for Markov model from CPRD

	Females (mean)	Males (mean)
Healthy		
80-84	2815	3123
85-89	3502	3884
90-94	4051	4460
95-99	4488	4891
100+	3705	3754
Coronary Heart Disease		
80-84	4085	4635
85-89	5032	5702
90-94	5807	6509
95-99	6516	7254
100+	6179	6609
Stroke		
80-84	4433	5150
85-89	5419	6316
90-94	6222	7114
95-99	6940	7798
100+	6521	6993
Diabetes Mellitus		
80-84	3818	4487
85-89	4783	5567
90-94	5539	6427
95-99	6288	7071
100+	6898	5896
Falls		
All ages		1299.70

Supplementary Table 3: Intervention effects for Markov model

Condition	Mean Relative Risk (RR)	95% CI	Source
Incidence			
Coronary heart disease	0.66	0.53 to 0.82	*Beckett et al. 2008 (HYVET Main Trial)*
Stroke	0.70	0.49 to 1.01	*Beckett et al. 2008 (HYVET Main Trial)*
Diabetes mellitus	1.00	1.00 to 1.00	*N/A*
Falls	1.40	1.03 to 1.90	*Tinetti et al. 2014*
Mortality			
Coronary heart disease	0.77	0.60 to 1.01	
Stroke	0.61	0.38 to 0.99	*Beckett et al. 2008 (HYVET Main Trial)*
Diabetes mellitus	0.79	0.65 to 0.95	
All cause death	0.79	0.65 to 0.95	

Supplementary Table 4: Utility values for health states used in the model

	Mean	Standard Error	Source
Coronary heart disease	0.648[a]	0.02	*Sullivan et al. 2011, ICD-9 414 (Web Table 5 + age decrement)*
Stroke	0.516	0.02	*Sullivan et al. 2011, ICD-9 436 (Web Table 5 + age decrement)*
Diabetes mellitus	0.656	0.006	*Sullivan et al. 2011, ICD-9 250 (Web Table 5 + age decrement)*
Healthy	0.818	0.008	*Sullivan et al. 2011, MEPS General mean EQ-5D score (Web Table 1 + age decrement)*
Age decrement	-0.00027	0.0002	*Sullivan et al. 2011, Age disutility covariate (Web Table 4)*

[a] CHD utility at age 80 (using age decrement) = 0.651357[ICD-9 414, age 67] + (-0.00027*13)